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Modeling Approach: Ozone

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HAZARD ASSESSMENT USING AN INTEGRATED PHYSIOLOGICALLY-BASED
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16. ABSTRACT A physiologically-based dosimetry modeling approach can provide a framework for integrating various components of hazard assessment to obtain interspecies dose-response curves as part of the risk assessment process. The methodology presented for developing dose-response curves is illustrated within the context of the inhalation toxicology of a ubiquitous air pollutant, ozone. Major components of the approach are discussed, including a data-based management system, the Critical Toxicity Reference System, and a physiological based dosimetry model for ozone absorption in the lower respiratory tract of mammals. Features and characteristics of the two components are discussed. The methodology of the physiologically-based dosimetry modeling approach is illustrated by application to ozone-induced edema in rats. Consolidated results from several laboratories using different exposure times, concentrations, animal sizes, and experimental methods were used to obtain a single dose-response relationship to increased lung weight versus estimated pulmonary ozone tissue dose. When the ozone dosimetry modeling approach is sufficiently developed, it can provide improved estimates for dose-response relationships in experimental animals, leading to improved estimates of human health risks.		
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INTRODUCTION

In examining the possible role of pharmacokinetics and pharmacodynamics in risk assessment, the underlying philosophy of the legislative mandate through which the risk assessment will be applied must be kept in mind. For example, the ability of the Food and Drug Administration to invoke the Delaney Clause to regulate a substance is different from the risk assessments required for the Environmental Protection Agency's National Ambient Air Quality Standards (NAAQS). The kind and level of information that is available can vary greatly. Reevaluation of the NAAQS for ozone (O_3) focuses on whether or not the value of the standard should be changed by as little as 20 percent, while many carcinogenic risk assessments are trying to establish the level of risk to within one to two orders of magnitude. In any case, the uncertainties identified in risk assessments help to establish areas in which additional research would be useful.

The intent of this paper is to broaden awareness that pharmacokinetics and mathematical dosimetry models are useful tools in risk assessments of noncarcinogenic as well as carcinogenic effects. While examples of modeling applications have been predominantly related to carcinogenesis, health effects such as emphysema and fibrosis are not to be ignored. This is particularly true for oxidant gases. For example, several animal studies in different species show that long-term exposure to nitrogen dioxide produces emphysema (Fenters et al., 1973; Hyde et al., 1978; Riddick et al., 1968), and O_3 causes pulmonary fibrosis (Fujinaka, et al., 1985). Moreover, subchronic exposures at relatively low levels of these gases have been shown to lead to cellular changes (Barry et al., 1985 and Chang et al., 1986) that are indicative of a structural remodeling of the lung. The impetus is clear that man must

be protected from such effects. But in order to use the animal toxicological data more quantitatively in setting appropriate NAAQS for these gases, extrapolation modeling is required.

We have discussed at this Workshop the need to incorporate pharmacodynamics in the modeling process. Thus far, most risk assessments have assumed a priori that an equivalency of response exists between animals and man. As one proceeds from the molecular level or biochemical event towards injury at the tissue or organ level, that assumption becomes less tenable because of possible species differences in repair processes, levels of anti-oxidant enzymes, etc. Dose, if it is sufficiently high, can produce damage anywhere from the molecular to the organ level. On the other hand, various host defense systems can interact, and if the damage is not sufficiently severe, yield recovery. If the delivered dose overwhelms these defense systems, various disease states can result. Defense systems might conceivably play a role in the etiology of lung disease. All of this is a dynamic situation.

Figure 1 (based on Figure 1-1 of National Research Council, 1983) summarizes an overview of the research, risk assessment and risk management processes, and their interrelationships that lead to the recommendation of a NAAQS. The present work focuses on the phases of the processes outlined by the dashed rectangle. Here, the area of pharmacokinetics offers great potential for improved risk assessments, particularly when these assessments are required to be more quantitative in nature. The development of dosimetry models that can provide a description of the uptake and distribution of chemical compounds throughout the body, and the availability of toxicological data that can be used to establish dose-response relationships is integral to these efforts. Incorporating laboratory and field observations of adverse health effects, hazard information, and extrapolation methods to yield dose-response assessments is critical to the risk assessment process. The combining of these phases can

be facilitated by the integrated physiologically-based dosimetry modeling approach, illustrated schematically in Figure 2.

The major components of the approach are the Critical Toxicity Reference (CTR) System (Smolko et al., 1986) and the Physiologically-Based Dosimetry (PBD) model. The CTR System is comprised of four elements: (1) searching the literature for references reporting toxicity data relevant to the toxicant being studied; (2) abstracting information from the selected references in a form appropriate for both quantitative and descriptive extraction; (3) constructing a data base which consists of bibliographic and abstracted information; and (4) compiling concentration-response data by a series of searches of the developed data base. The primary factors considered in developing PBD models are mammalian physiological processes, anatomical characteristics, physicochemical properties of the gas and of relevant biochemical constituents, and mass transport processes. PBD model predictions of dose, appropriate for species with the specific characteristics described in the literature, are combined with the concentration-response data which have been collated by species and endpoint. The resulting dose-response relationships can utilize various expressions of dose to obtain the most appropriate quantitative representation of toxicological effects.

The analyses can incorporate species sensitivity information for consideration of such factors as host defense, repair processes, and genetics. One outcome of this approach is an estimation of human toxicity which can be used as input into the risk assessment and risk management processes. A second outcome is information to aid in identification of data gaps and design of experiments. This latter outcome is particularly important because it can eventually yield new data that will be used in the iterative application

of the integrated PBD model approach which will strengthen the overall risk assessment and risk management processes.

The remaining sections of this paper illustrate the integrated PBD modeling approach (Figure 2) by applying data from the CTR system and predictions from a PBD model for O_3 to construct dose-response relationships. This will be done first by discussing the formulation, as well as sample simulation results, of a PBD model that predicts the uptake and distribution of absorbed O_3 in the lungs of mammals. While the focus will be on O_3 , the intent is primarily to illustrate the methodology and to provide an understanding of various aspects of delivered dose. The methods discussed will be particularly important when some of these procedures are extended to volatile organic compounds, for which first-pass metabolic effects in the lung are a concern. Also, a brief discussion is provided of a data base management system, CTR, that has been developed to store and retrieve quantitative data in a manner useful for mathematical dosimetry models. An application to ozone toxicological data is presented to illustrate the methodology of using mathematical dosimetry models to examine quantitative dose-response relationships.

LOWER RESPIRATORY TRACT MATHEMATICAL DOSIMETRY MODELING

In this Workshop, much attention is being placed on the use of physiologically-based pharmacokinetic models to provide a description of dose distribution following inhalation of a chemical compound. To date, these models predict average levels of the chemical throughout an entire organ (or body compartment). However, as illustrated below, additional complexities are involved when evaluating the distribution of inhaled gases within the lower respiratory tract (LRT), where dose in various lung regions can vary greatly, and consequently have different health effect outcomes.

Model Conceptualization

The major factors affecting the regional uptake of O_3 are morphology of the respiratory tract, the route of breathing, the depth and rate of breathing, gaseous physicochemical properties, the physical processes governing gas transport, and the physicochemical properties of the tracheobronchial (TB) liquid lining and of the air-blood barrier in the pulmonary region. All these factors interact in a complex way to determine dose and must be considered in developing a simulation model.

The mathematical model formulation will focus on the lower respiratory tract for several reasons. Upper respiratory tract removal of inhaled gases and particles is amenable to experimental determination of deposition (Yokoyama, 1968; Yokoyama and Frank, 1972; Corn et al., 1976; Miller et al., 1979). The morphology of the upper respiratory tract is quite complex, difficult to measure, and variable between species (Schreider and Raabe, 1981; Schreider, 1986), so mathematical descriptions are difficult to obtain. Further, airflow patterns are also complex (Patra et al., 1986), so proper treatment of gas transport processes is not apparent. However, experimental values for upper respiratory tract uptake of the inhaled gas can provide appropriate boundary conditions for mathematically modeling delivered doses to LRT regions.

Aspects of LRT structure and their relationship to model compartments are illustrated in Figure 3. Briefly, anatomical descriptions of the lung are needed such as those available for man (e.g., Wiebel, 1963; Yeh and Schum, 1980) and for various animals (e.g., Kliment, 1973; Yeh et al. 1979, Schreider and Hutchens, 1980). The top portion of Figure 3 shows Weibel's representation of the TB and pulmonary regions of the human lung. For mathematical modeling purposes, we conceptualize this representation into a series of right circular cylinders, and information is needed on the lengths, diameters,

and radii of the TB airways. In the pulmonary region, data on the structure of the pulmonary ducts and sacs, and on the number of alveoli, their surface areas, and volumes are necessary to apply the model description of gas transport processes.

In the TB or conducting airways, a mucociliary layer protects the underlying ciliated, goblet, brush, and basal cells, etc. from direct insult by the inhaled gas. As can be seen in Figure 3, this layer is comprised of an epiphase and a hypophase. Lacking definitive data on the thickness and chemical composition of these phases in various portions of the TB region, the current model formulation combines them into one compartment. For ambient exposures to the highly reactive gases, such as O_3 , penetration to the bloodstream in the TB region can be ignored (see Miller et al., 1985 for details). Thus, in the TB region, model compartments correspond to the air, liquid lining layer, and underlying tissue. However, for highly soluble and nonreactive gases, a blood compartment and a description of the fate of the gas in other organs and compartments of the body probably would be needed.

In the pulmonary region, the epithelium is chiefly comprised of Type I and Type II cells over which a very thin layer of a surfactant fluid can be found. Underlying the epithelium are the interstitium and the endothelial cells of the capillary network. Since the alveoli are arranged "back to back", with capillaries between them, the model formulation for the air, liquid lining tissue, and blood compartments is assumed to be symmetrical (Figure 3).

To examine gas transport in the airways, the three-dimensional equation of continuity is simplified by appropriate integrations and averagings to obtain a one-dimensional equation of mass transport. The processes of axial convection and axial dispersion, the loss of O_3 to the liquid lining, and lung expansion and contraction are taken into account. Lung expansion and contraction during

the breathing cycle become important when modeling pollutant uptake for minute ventilations corresponding to heavy exertion. When modeling mass transfer in the liquid lining, tissue, and blood compartments, the transport of ozone is related to molecular diffusion and chemical reaction terms. The reader is referred to Figure 2 of Overton et al. (1987b), in this book, for explicit forms of the partial differential equations used in the model. For a detailed discussion of the model formulation and assumptions, as well as the basis for these assumptions, the reader is referred to Miller et al. (1985) and Overton et al. (1987a). Note that when modeling other gases, modifications of the expression for loss of the gas to airway walls may be necessary. In addition, high solubility or non-reactivity may necessitate changes in some aspects of treating gas transport in the airways.

Information required to model adequately transport in the mucus or surfactant lining liquid, tissue, and blood compartments includes quantitative biochemical data on the constituents as well as on the chemical reactions of O_3 with these constituents. Currently, a pseudo first-order reaction scheme is assumed when modeling ozone uptake (see Miller et al., 1985). Estimates of liquid lining, tissue, and blood compartment thickness are also required. At present, this is an area in which most of the available information is from animal studies. Data for man are very limited, and assumptions about the distribution of compartment thickness must be made. Compartmental diffusion coefficients and partition coefficients, such as those used in physiologically-based pharmacokinetic models, are also needed. Much of the above topic is discussed in detail elsewhere (Miller et al., 1985; Overton et al., 1987a).

Examples of O₃ Dosimetry Modeling Results

Utilizing the model formulation concepts discussed above, Miller et al. (1985) examined the uptake of O₃ in the LRT of man and performed various sensitivity analyses to illustrate the importance of LRT secretions on delivered dose. This work shows that the net amount of O₃ removed in the trachea can be several orders of magnitude different from the amount of O₃ that penetrates to the underlying tissue. Proceeding distally from the trachea, this difference diminishes mainly because of the decline in the thickness of the liquid lining. Furthermore, since the gas exchange region is lined with a very thin fluid which does not contain many constituents that react with O₃, the net amount of O₃ removed and the tissue dose of O₃ are essentially the same. According to Miller et al. (1985), the net O₃ dose curves are much less dependent on the thickness of the TB liquid lining than are the O₃ tissue dose curves.

Another example of sensitivity analysis demonstrating the importance of model parameters is concerned with the values of the liquid lining rate constants. Simulations show that the effect of increased chemical reactivity in the TB liquid lining is to increase the net airway doses in the TB region and to decrease the tissue dose throughout the LRT. Furthermore, tissue dose is found to be much more sensitive to the TB liquid lining reactions than is the net dose. For example, the tracheal tissue dose is predicted to decrease by about three orders of magnitude, and the tracheal net dose is predicted to increase by about one order of magnitude, due to a rate constant change from zero to twice the reference value. However, pulmonary net and tissue dose values are predicted to change by less than a factor of two as a result of the same change in the TB liquid lining rate constant. By contrast, changes in the pulmonary liquid lining rate constant lead to simulation results

for LRT net and tissue doses that are essentially unchanged from those obtained with the reference values. These types of analyses show that in order to determine dose-effect relationships for various cell types or components (e.g., cilia) in the conducting airways, better quantitative data than are presently available on TB liquid lining rate constants and thickness are desirable. On the other hand, the lower sensitivity of predicted pulmonary doses to parameter uncertainties gives a greater confidence in making interspecies comparisons of dose-effect relationships in this region compared to making such comparisons in the TB region.

An example of interspecies dosimetric comparisons is illustrated in Figure 4 in which the solid and dashed lines are O_3 dosimetry simulation data for the rat and man, respectively. Predictions for the rat lung use the Yeh et al. (1979) anatomical model wherein the morphometric data are represented in a generational type model analogous to the Weibel (1963) generational morphometric data for the human lung. Both the net and tissue dose of O_3 are shown for these species. Dose is expressed in Figure 4 as micrograms of O_3 per square centimeter of airway surface area per minute, standardized to a tracheal O_3 value of $1 \mu\text{g}/\text{m}^3$. Thus, for a tracheal concentration of $1000 \mu\text{g}/\text{m}^3$, the predicted airway doses are 1000 times the plotted values; for a tracheal concentration of one part per million multiply the plotted values by 1960 ($\mu\text{g}/\text{m}^3$ per ppm).

As can be seen from Figure 4, the net removal of O_3 is very comparable in the rat and human lung. To help examine tissue dose patterns, we have matched the first generation of respiratory bronchioles in man with the first alveolated airway in the rat lung. This region is where the histopathological data show the first and the most pronounced lesions in O_3 toxicological

studies using rats (Stephens et al., 1973, 1974; Plopper et al., 1979; Boorman et al., 1980; Barry et al., 1985). The maximal dose in both man and rat is predicted to occur at this particular region. Almost a 10-fold increase in deposition or removal of O₃ is predicted in this region in the rat compared to man according to the dose curves shown in Figure 4 which are standardized to a unit tracheal O₃ value. However, to make more definitive interspecies dosimetric comparison at this point, nasopharyngeal removal of O₃ in man versus rat must be considered. Nasopharyngeal removal studies are currently being conducted, and when available, will facilitate translation of the net and tissue dose curves of Figure 4 into delivered dose curves associated with exposure to O₃.

CRITICAL TOXICITY REFERENCE SYSTEM

Data collection for the O₃ analyses was accomplished via the CTR System (Smolko et al., 1986). The four basic elements of this System have been briefly described. Sources of references for inclusion in the CTR data base includes searches of nationally available data bases (e.g., National Library of Medicine), comprehensive documents, personal communication with colleagues working with the toxicant being studied, and personal review of the relevant literature. Upon establishing an initial base of information from a thorough literature search, the same sources are used to update periodically the CTR data base. A coding strategy was developed to provide a mechanism for retrieving specific data required for dose-response analyses. All information is abstracted onto a coding sheet according to a pre-determined format. Abstractors are intensively trained and assist in all aspects of this phase upon completion of their training. Information abstracted onto the coding sheet is entered into the computerized data base. Each reference comprises a unique file and is assigned a unique identification number.

A critical element for dose-response analyses is a quantitative representation of the effect observed and reported in the literature. The last phase of the CTR System, then, compiles the concentration-response data in a form useful for combination with the PBD model predictions. Sub-data bases are generated for easy access to subsets of information or to facilitate future searches for very specific information. For example, a sub-data base could be established for all references reporting concentration-response data. This could subsequently be searched to sort by animal species. Further searches of these sub-data bases could identify studies of particular biological endpoints at specific pollutant concentrations.

After the concentration-response data are compiled, individual studies are examined for inclusion in the dose-response analyses. The basic criteria applied include: a quantitative representation of effect; the use of a species appropriate for combination with the PBD Model for O_3 ; an adequate presentation of data; a statistical analysis of data; exposures to O_3 only; a lack of variables which might confound results; and continuous exposures to a single concentration of O_3 . Other items considered when selecting studies concerned both interpretive and technical quality. Interpretive quality criteria addressed items such as using an appropriate experiment to test the hypothesis, while technical quality criteria addressed items such as providing precise descriptions of experiments and data analysis.

When specific studies appropriate for dose-response analyses are identified, information regarding weight, etc. of the species used is extracted. These data are used with the PBD model to predict the dose of O_3 reaching specific regions of the lung. Figure 5 shows PBD model predictions of dose to the mucus lined tissue, the surfactant lined tissue, and the total lung for rats (using the anatomical model of Yeh et al., 1979) exposed to $1960 \mu g/m^3$ (1 ppm) O_3 .

Combining dosimetry data, such as those contained in Figure 5, with biological effects data to yield dose-response curves will be illustrated using the formation of edema as an endpoint. Experimental studies (Nambu and Yokoyama, 1981; Maltani and Suzuki, 1981; Suzuki, 1976; Ichikawa and Yokoyama, 1982) were selected in which edema formation was indicated by an increase in lung wet weight. Since nasopharyngeal removal of O_3 in the rat has not been experimentally determined, one analysis was conducted assuming 10% removal of O_3 in the head and another assuming 25% removal. Unconfirmed preliminary experiments (Drs. Jean Wiester and Gary Hatch, personal communication), indicate that the rat may remove 10-25% of the inhaled O_3 in the nasopharyngeal region. Because edema is generally considered to reflect injury to gas-exchange regions, pulmonary tissue dose was used in the dose-response analysis (Figure 6). Data points represent various combinations of exposures to O_3 concentrations ranging from 1 to 5 ppm for durations ranging from 3 to 12 hours. While a linear fit to the dose-response data is depicted in Figure 6, other curves may be equally plausible to describe the dependence of increased lung wet weight on the dose of O_3 delivered to the pulmonary region of the rat. The next step in the analysis would be to determine, using the PBD model, which O_3 exposure profiles would result in comparable predicted doses of O_3 in the human lung. This would allow better judgments on the reasonableness of extrapolating to man the toxicological data on edema in rats following exposure to O_3 .

SUMMARY

Determining tissue dose is a fundamental starting point when making interspecies dose-response comparisons. Due to the complexity and cellular diversity of the lung, toxicologically relevant lung dosimetry needs to be related to specific sites within the respiratory tract to achieve a better understanding of the tissue dose dependence on toxicity of inhaled pollutants. Direct measurement of tissue or cellular dose by radiometric, physical, or chemical means within specific segments of the lung is one approach to determining equivalent doses between species. However, such experiments are inherently limited since providing experimental data on all exposure situations of interest for hazard assessment is practically impossible and obtaining such a broad data base in man is ethically impossible. One approach to this problem is to develop mathematical dosimetry models of the lung which take into account not only the physical and chemical properties of the inhaled toxicant, but also the anatomical and physical properties of the lung of the exposed animal species or man. This approach, with dose predicted by respiratory tract region or airway generation provides: 1) a guide for future biological experimentation, 2) a framework for further refinement and validation of the assumptions of mathematical dosimetry models, and 3) a basis for quantitative inter- and intraspecies comparisons of toxicological results.

A data base management system is available to store and retrieve quantitative data in a manner useable as input files in dosimetric models. The effects of O₃ on all studied organ systems have been encoded, and citations reporting health effects are retrievable. Scaling for age, weight, sex, and species for critical characteristics are provided to yield appropriate data to use in conjunction with the PBD model for O₃. Predicted dose and toxicological response are combined to establish dose-response relationships. The methodology

was illustrated for pulmonary edema wherein results from several laboratories using different exposure times, concentrations, animal sizes, and experimental methods were consolidated to obtain a single dose-response relationship. Ultimately, when the O₃ dosimetry modeling approach is sufficiently developed, it can provide an improved basis for estimating dose-response relationships for toxic effects observed in experimental animal studies for the purpose of estimating human risk. These assessments, in turn, can serve as an important input to risk management decisions concerning the regulation of O₃.

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FIGURE LEGEND

- Figure 1. Major elements of risk assessment and risk management. Phases of the process which can be addressed using an integrated physiologically-based dosimetry modeling approach are contained within the dashed rectangle. Overall figure schematic is based on Figure 1-1 of National Research Council (1983).
- Figure 2. A schematic of the elements of an integrated physiologically-based dosimetry modeling approach to estimating human toxicity that leads to one of the components of risk characterization. The procedure diagrammed in the dashed rectangle is the proposed approach for implementing the dashed rectangle process in Figure 1.
- Figure 3. The relationships between morphologies and their model representations. Panel a is a schematic of the branching airways of the TB and pulmonary region of man (based on Weibel, 1963). The generations are labeled from the right, beginning with the trachea. BR, BL and TBL indicate bronchi, bronchioles and terminal bronchioles, respectively; the respiratory bronchioles, alveolar ducts, and alveolar sacs are indicated by RBL, AD and AS, respectively. Below the TB portion of the lung schematic are three cylindrical figures that indicate the model representation of the airways. Panel c shows a diagram of the structure of the liquid lining and tissue of the TB region (diagram based on Jeffery and Reid, 1977). The different cells represented are basal (BC), ciliated (CC), brush (BrC), goblet (GC), and nonciliated serous (NCC). Panel e illustrates the model representation of TB liquid lining and tissue compartments. On the left side of the figure, Panel b, is an electron micrograph of the interalveolar septa (based on Gehr et al., 1978). The air spaces (A), capillaries (C), type I cells and their nuclei (EP1 and NEP1), endothelial cells and their nuclei (EN and NEN), and interstitial space (IN) are indicated. Panel d illustrates the model representation of the liquid lining, tissue and capillaries of the pulmonary region.
- Figure 4. An example of a way of comparing species doses by plots of airway dose versus generation for two species, man (dashed curves) and rat (solid curves). The first generations of the pulmonary regions (17 and 16 in the anatomical models for man and rat, respectively) have been matched at the dotted vertical line to allow a better comparison of equivalent regions; this results in the break in the rat generations along the abscissa. The tidal volume (V_T) and breathing frequency (f) are given on the figure. Tissue dose is the predicted dose of the epithelial layer in the tracheobronchial region and of the air-blood barrier in the pulmonary region. Net dose is the total absorbed by the liquid lining, tissue, and blood compartments.

Figure 5. Predicted quantity of absorbed O_3 per breath versus rat weight for 1 ppm exposure concentration with 25% upper respiratory tract removal. The three curves are for total lower respiratory tract (X), tracheobronchial region tissue (□), and pulmonary region tissue (Δ) absorption. Predictions were made using the PBD model described in the text. Lower respiratory tract anatomical dimensions were based on Yeh et al., (1979) for a 330 g rat. Allometric equations were used to extrapolate the lung dimensions to those corresponding to other weights

Figure 6. Estimated dose-response curves. Percent increased lung weight due to O_3 exposure versus predicted pulmonary O_3 tissue dose per rat body weight resulting from 25% (○, dashed line) and 10% (■, solid line) upper respiratory tract removal is plotted. Dose is the total quantity of O_3 absorbed per body weight during exposure. Curves are fit by linear regression. Data from the CTR data management system, such as breathing frequency, time of exposure, animal weight, increased lung weight, and exposure concentration, combined with the PBD model predictions, as plotted for 25% head removal in Figure 5 and in other similar figures, were used to construct this figure.

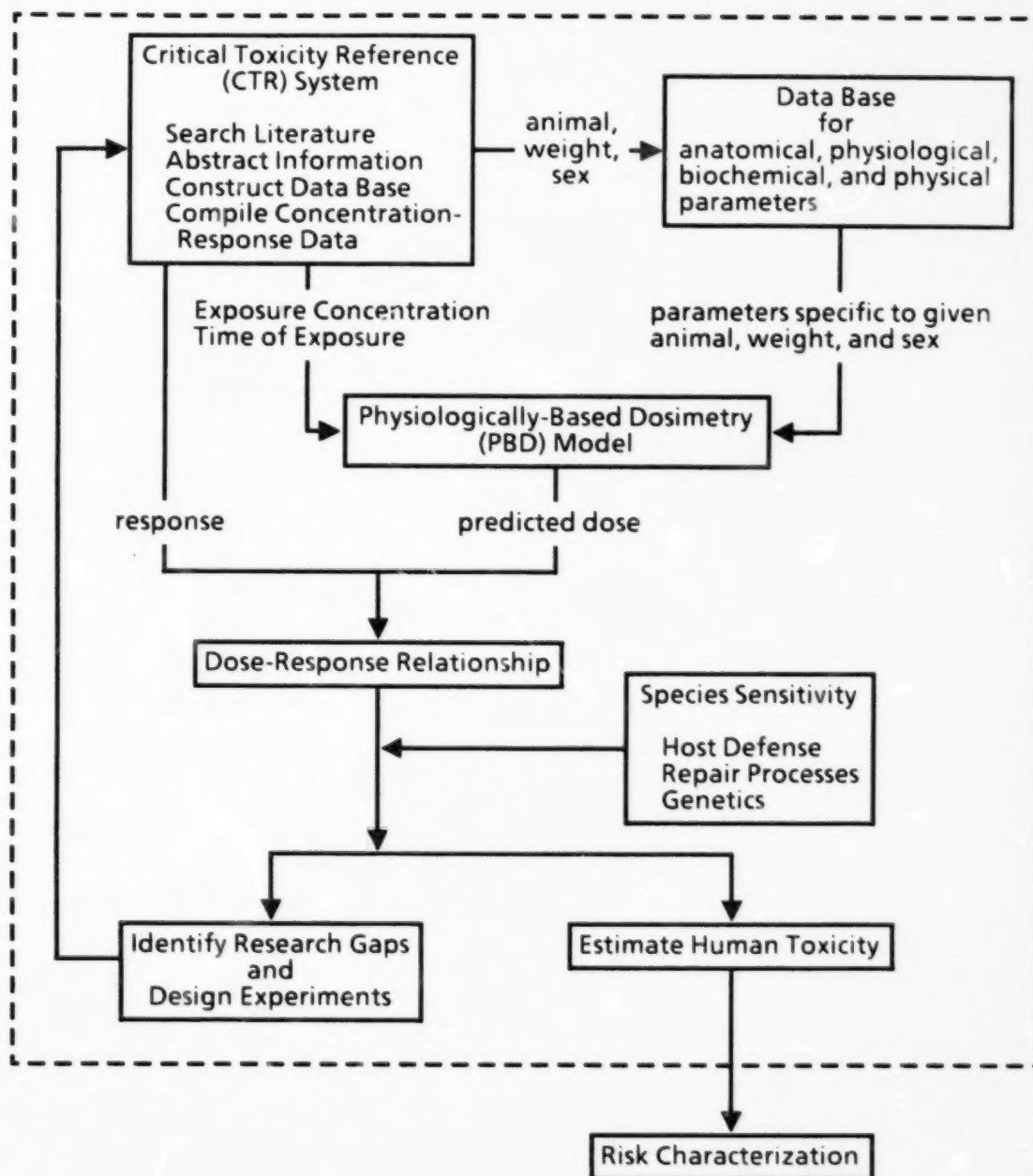


Figure 1.

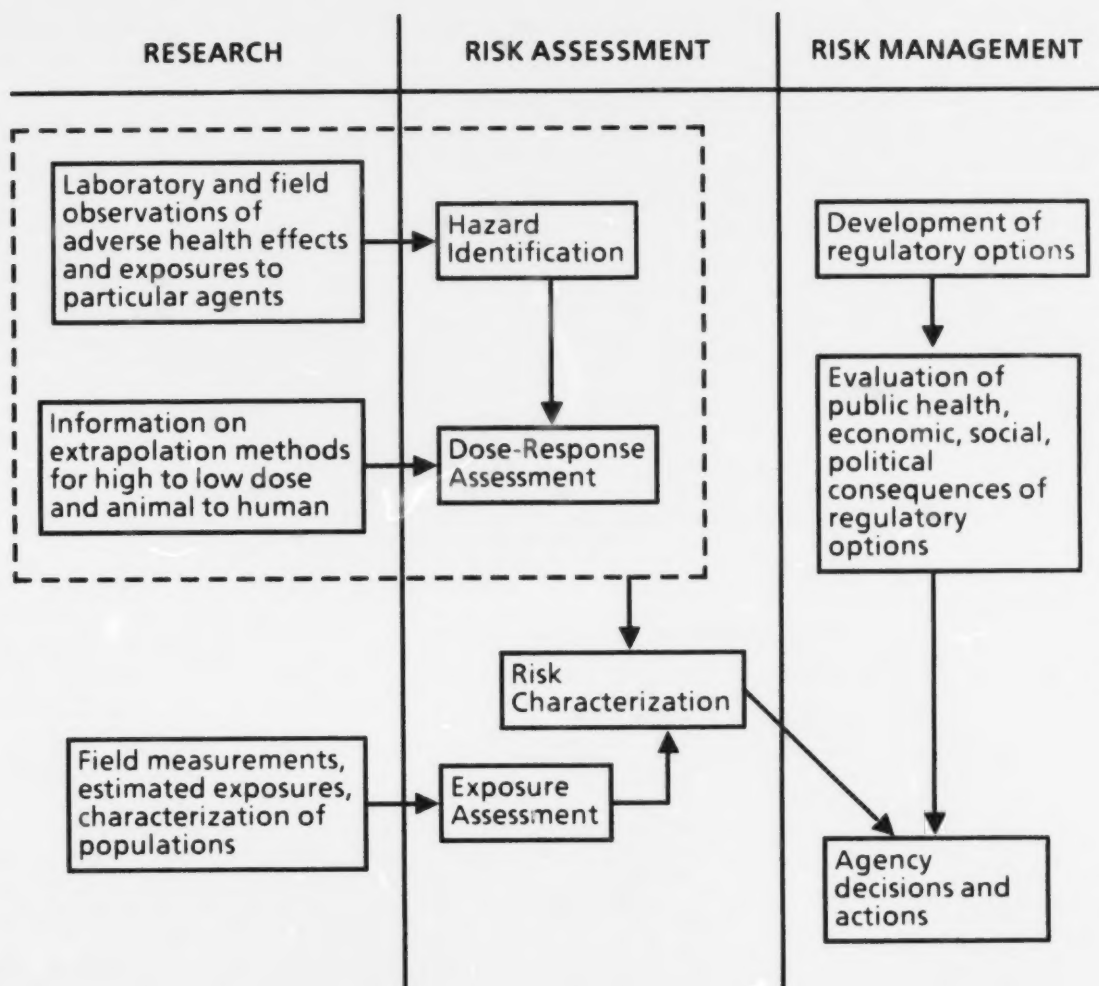


Figure 2.

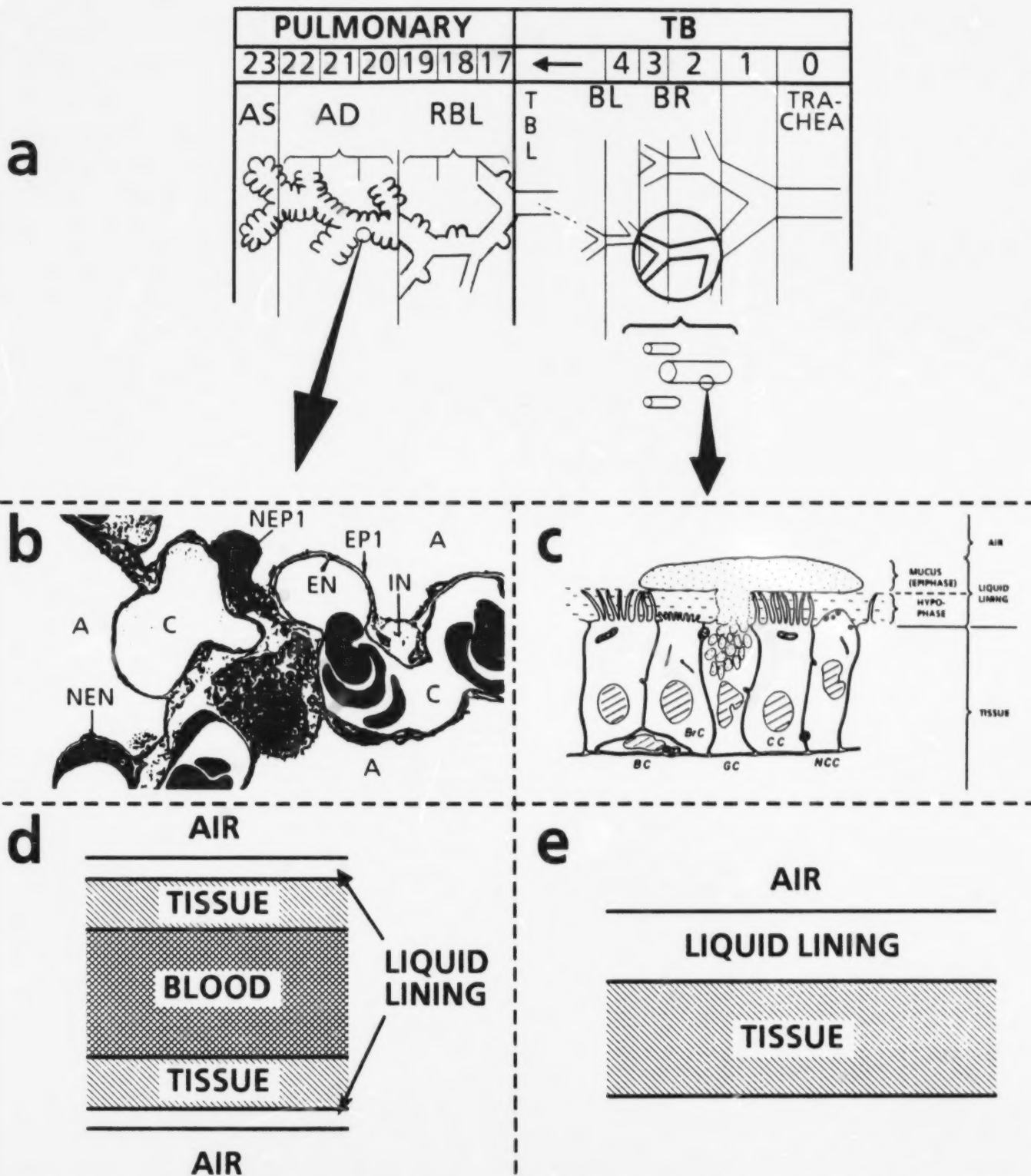


Figure 3.

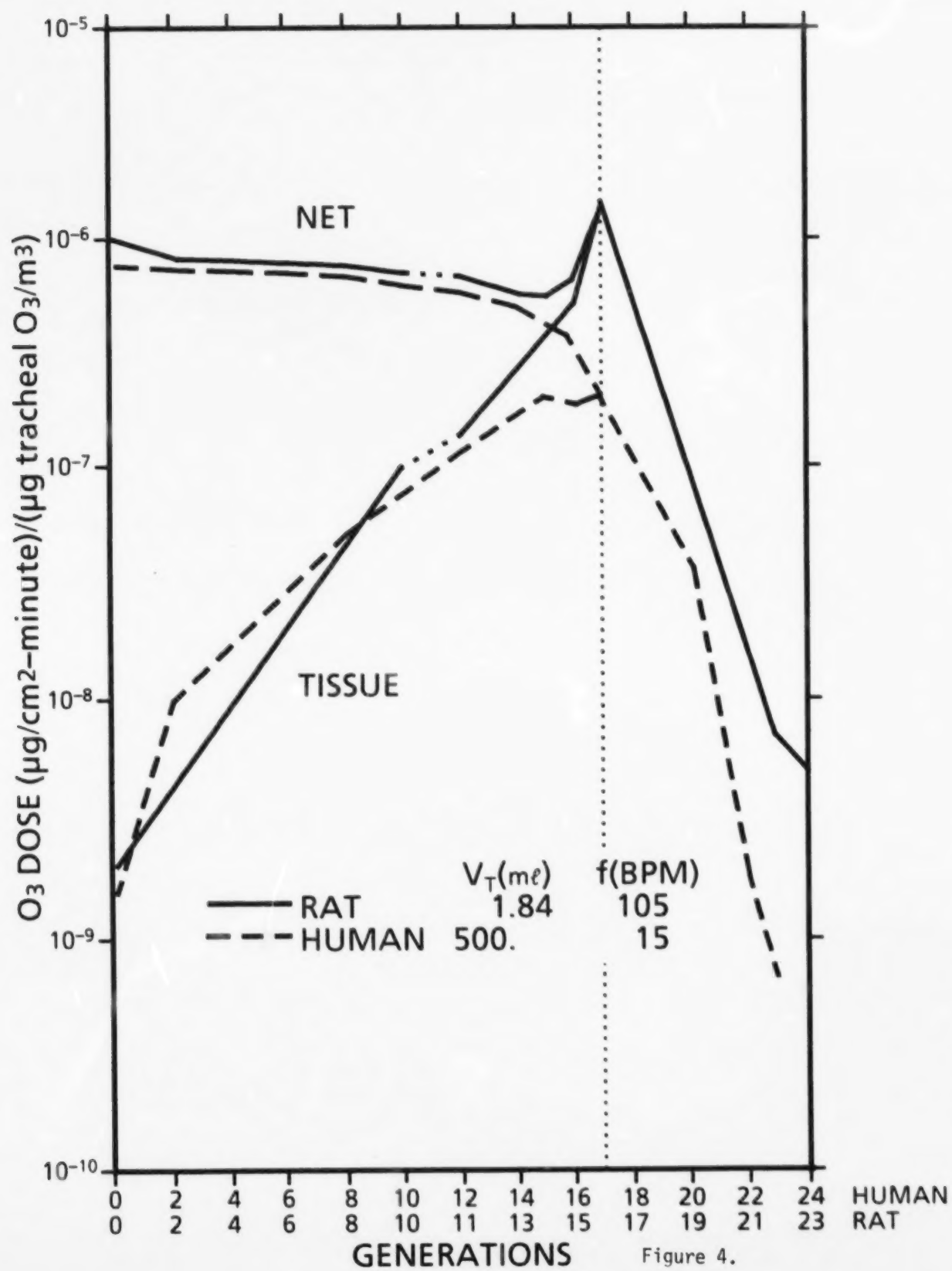


Figure 4.

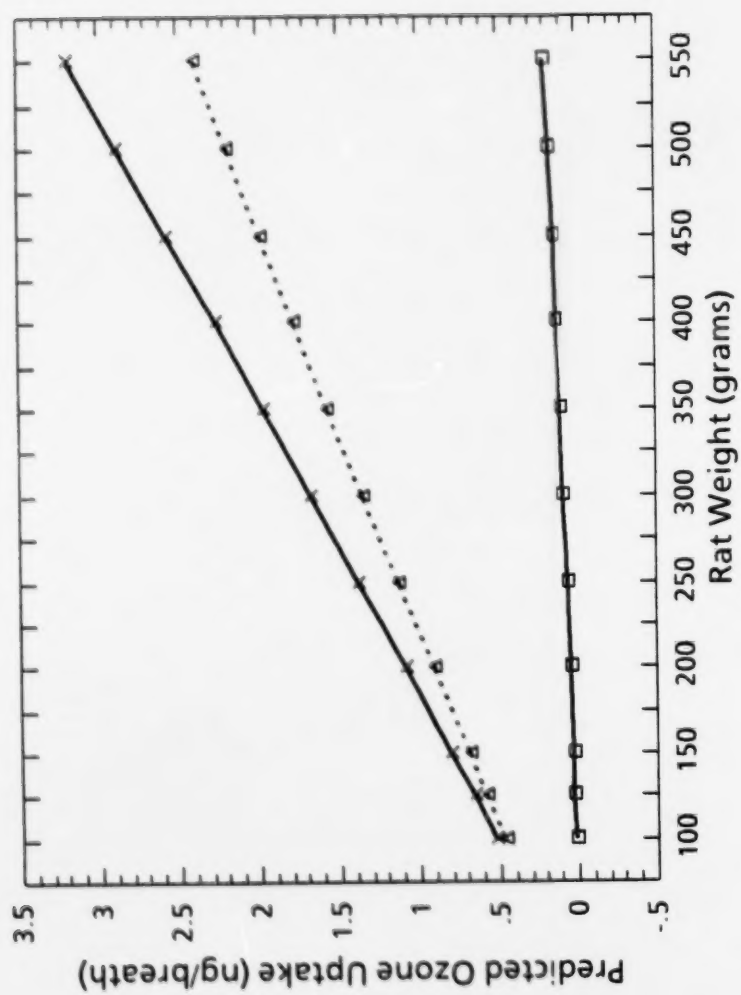


Figure 5.

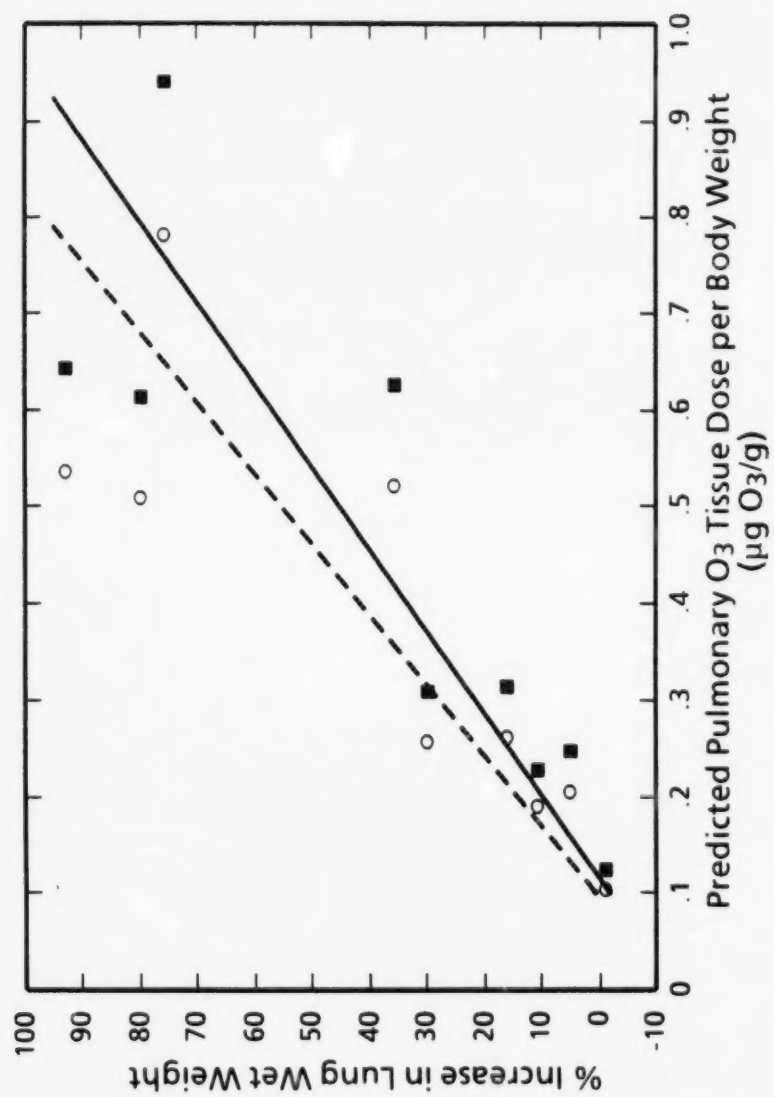


Figure 6.